UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/269,573	07/16/99	HAYASHIZAKI Y	024705-083

021839 HM12/1002
BURNS DOANE SWECKER & MATHIS L L P
POST OFFICE BOX 1404
ALEXANDRIA VA 22313-1404

EXAMINER	
FORMAN, B	
ART UNIT	**PAPER NUMBER**
1655	

DATE MAILED: 10/02/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/269,573	Applicant(s) HAYASHIZAKI, YOSHIHIDE	
	Examiner BJ Forman	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25 and 27-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25 27-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to papers filed 30 July 2001 in Paper No. 21 in which claims 1, 2, 4, 5, 7-9, 11, 15, 18, 23-25, 27, 32 and 33 were amended. All of the amendments have been thoroughly reviewed and entered. The previous rejections in the Office Action of Paper No. 19 dated 23 March 2001 under 35 U.S.C. 112, second paragraph and 35 U.S.C. 102(b) are withdrawn in view of the amendments and arguments. The previous rejections under 35 U.S.C. 103(a) are maintained. All of the arguments have been thoroughly reviewed and are discussed below.

Currently claims 1-25 and 27-30 are under prosecution.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-4, 19-21, 28-32 are rejected under 35 U.S.C. 103(a) as obvious over Wagner et al. (WO 93/02216, published 4 February 1993).

Regarding Claim 1, Wagner et al. teach a method for detecting nucleic acid fragment having a mutation comprising: hybridizing at least one nucleic acid fragment, with at least one nucleic acid fragment of which a mutation is to be assayed; binding a labeled substance, said substance specifically binding to a mismatched base pair occurring between the hybridized fragments; and identifying a fragment bound by the labeled substance by detecting the label to

thereby detect a nucleic acid having a mutation (page 6, lines 1-25) wherein the at least one fragment is fixed on a substrate (page 7, lines 4-8) and wherein the fragment fixed on the substrate (i.e. hybridization partner) is DNA prepared from any of source using any known technique e.g. naturally occurring DNA (page 16, lines 21-25). The preceding rejection is based on judicial precedent following In re Fitzgerald, 205 USPQ 594 because Wagner et al. is silent with regard to the hybridization partner having all of a sequence of a full-length gene. However, the sequence of a full-length gene recited in Claim 1 is deemed to be encompassed in the DNA hybridization partner teaching of Wagner et al. because DNAs prepared from naturally occurring DNA using known techniques, inherently encompasses full-length sequences. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the DNA fixed on the substrate of Wagner et al. by fixing a full-length gene sequence on the substrate for the obvious benefit of detecting any and all mutations in a gene within a genomic sample. The burden is on applicant to show that the claimed full-length gene is non-obvious over that of Wagner et al.

Regarding Claim 2, Wagner et al. teach the method wherein the substance specifically binding to a mismatched base pair is a mismatch binding protein (page 6, lines 13-17).

Regarding Claim 3, Wagner et al. teach the method wherein the mismatch binding protein is MutS (page 6, lines 29-31).

Regarding Claim 4, Wagner et al. teach the method wherein the substance specifically binding to a mismatched base pair is labeled with at least one kind of substance selected from the group consisting of luminescent proteins, phosphorescent proteins, fluorescent proteins, luminescent substances, fluorescent substances, phosphorescent substances, radioactive substances, stable isotopes, antibodies, antigens enzymes and proteins (page 27, lines 22-32).

Regarding Claim 19, Wagner et al. teach the method wherein the fragments of nucleic acid are bound to the substrate only at their 5' or 3' end i.e. via terminal phosphate groups or hydroxyl terminus (page 19, lines 20-33).

Regarding Claim 20, Wagner et al. teach the method wherein the fragments of nucleic acid are fixed on the substrate by covalent bonds (page 19, lines 9-10).

Regarding Claim 21, Wagner et al. teach the method wherein said nucleic acid is cDNA i.e. the immobilized nucleic acid is cDNA (page 6, lines 25-26 and page 13, lines 6-9).

Regarding Claim 28, Wagner et al. teach an article comprising a substrate having a surface on which nucleic acid fragments having all of a sequence of a full-length gene (page 6, lines 25-28) wherein the fragments are fixed in a hybridizable condition (page 7, lines 4-9) and wherein the fragment fixed on the substrate (i.e. hybridization partner) is DNA prepared from any of source using any known technique e.g. naturally occurring DNA (page 16, lines 21-25). The preceding rejection is based on judicial precedent following In re Fitzgerald, 205 USPQ 594 because Wagner et al. is silent with regard to the hybridization partner having all of a sequence of a full-length gene. However, the sequence of a full-length gene recited in Claim 1 is deemed to be encompassed in the DNA hybridization partner teaching of Wagner et al. because DNAs prepared from naturally occurring DNA using known techniques, inherently encompasses full-length sequences. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the DNA fixed on the substrate of Wagner et al. by fixing a full-length gene sequence on the substrate for the obvious benefit of detecting any and all mutations in a gene within a genomic sample. The burden is on applicant to show that the claimed full-length gene is non-obvious over that of Wagner et al.

Regarding Claim 29, Wagner et al. teach the article wherein said fragments are bound to the substrate only at their 5' or 3' end i.e. via terminal phosphate groups or hydroxyl terminus (page 19, lines 20-33).

Regarding Claim 30, Wagner et al. teach the article wherein said fragments are bound to the substrate by covalent bonds (page 19, lines 9-10).

Regarding Claim 31, Wagner et al. teach the article wherein said nucleic acid is cDNA (page 13, lines 4-9).

Regarding (New) Claim 32, Wagner et al. teach a method for detecting nucleic acid fragment having a mutation comprising: providing at least one polynucleotide fixed on a substrate; a sample comprising at least one nucleic acid fragment of which a mutation is to be assayed; a labeled substance wherein said substance specifically binds to a mismatched base pair resulting from hybridization between a polynucleotide fragment and a fragment comprising a mutation; hybridizing said fragment to said polynucleotide; introducing said labeled substance to specifically bind to any mismatched base pairs; and identifying a fragment bound by the labeled substance to thereby detect a nucleic acid having a mutation (page 6, line 1-page 7, line 8) and wherein the fragment fixed on the substrate (i.e. hybridization partner) is DNA prepared from any of source using any known technique e.g. naturally occurring DNA (page 16, lines 21-25). The preceding rejection is based on judicial precedent following In re Fitzgerald, 205 USPQ 594 because Wagner et al. is silent with regard to the hybridization partner having all of a sequence of a full-length gene. However, the sequence of a full-length gene recited in Claim 1 is deemed to be encompassed in the DNA hybridization partner teaching of Wagner et al. because DNAs prepared from naturally occurring DNA using known techniques, inherently encompasses full-length sequences. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the DNA fixed on the substrate of Wagner et al. by fixing a full-length gene sequence on the substrate for the obvious benefit of detecting any and all mutations in a gene within a genomic sample. The burden is on applicant to show that the claimed full-length gene is non-obvious over that of Wagner et al.

Response to Arguments

4. Applicant argues that Wagner et al. do not teach or suggest the use of a DNA with the sequence of a full-length gene as a hybridization partner and Applicant points to Example III wherein the cDNA hybridization partners are prepared by standard methods (Sambrook). These arguments are not found persuasive because Wagner et al. specifically that teach their hybridization partner is prepared using any known techniques and from any source e.g. naturally occurring DNA. Therefore, it would have been obvious to one of ordinary skill in the

art at the time the claimed invention was made to modify the DNA fixed on the substrate of Wagner et al. by fixing a full-length gene sequence on the substrate for the obvious benefit of detecting any and all mutations in a gene within a genomic sample. The burden is on applicant to show that the claimed full-length gene is non-obvious over that of Wagner et al.

Applicants further argue that use of a full-length gene as a hybridization partner is incompatible with the "tiling methodology" of Wagner et al. This argument is not found persuasive because Wagner et al. clearly teach or suggest the invention as claimed and described above.

5. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wagner et al. (WO 93/02216, published 4 February 1993) in view of Zoltukhin et al. (U.S. Patent No. 5,874,304, filed 18 January 1996)

Regarding Claim 5, Wagner et al. teach a method for detecting nucleic acid fragment having a mutation comprising: hybridizing at least one nucleic acid fragment, with at least one nucleic acid fragment of which a mutation is to be assayed; binding a labeled substance, said substance specifically binding to a mismatched base pair occurring between the hybridized fragments; and identifying a fragment bound by the labeled substance by detecting the label, thereby detecting a nucleic acid having a mutation (page 6, lines 1-25) wherein at least one fragment is fixed on a substrate (page 7, lines 4-8) and has all of a sequence of a full-length gene (page 6, lines 25-27) and further introducing a label into a nucleic acid fragment to be assayed for mutations (by adding the labeled mismatch-binding protein) and detecting the label to identify the fragment having a mutation (page 6, lines 19-24) but they do not teach the mismatched base pair is labeled with GFP. However, GFP labeled proteins were known in the art at the time the claimed invention was made as taught by Zoltukhin et al. who teaches the advantages of GFP i.e. it does not require cofactors or substrates and it is small in size (Column 1, lines 52-59 and Column 8, lines 22-27). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the GFP label of Zoltukhin et al. to the labeled mismatched base pair binding substance of Wagner et al. for the

expected benefit of simplicity by eliminating need for cofactors and substrates as taught by Zoltukhin et al. (Column 1, lines 52-59 and Column 8, lines 22-27).

Response to Arguments

6. Applicant argues that Zoltukhin et al. do not remedy the deficiencies of Wagner et al. and therefore the combination of Wagner et al. and Zoltukhin et al. do not teach or suggest the claimed invention. This argument is not found persuasive for the reasons stated above in ¶ 4 i.e. it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the DNA fixed on the substrate of Wagner et al. by fixing a full-length gene sequence on the substrate for the obvious benefit of detecting any and all mutations in a gene within a genomic sample.

7. Claims 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wagner et al. (WO 93/02216, published 4 February 1993) in view of Gifford (U.S. Patent No. 5,750,335, filed 22 April 1993).

Regarding Claim 6, Wagner et al. teach a method for detecting nucleic acid fragment having a mutation comprising: hybridizing at least one nucleic acid fragment, with at least one nucleic acid fragment of which a mutation is to be assayed; binding a labeled substance, said substance specifically binding to a mismatched base pair occurring between the hybridized fragments; and identifying a fragment bound by the labeled substance by detecting the label, thereby detecting a nucleic acid having a mutation (page 6, lines 1-25) wherein at least one fragment is fixed on a substrate (page 7, lines 4-8) and has all of a sequence of a full-length gene (page 6, lines 25-27) and introducing a label into a nucleic acid fragment to be assayed for mutations (by adding the labeled mismatch-binding protein) and detecting the label to identify the fragment having a mutation (page 6, lines 19-24) but they do not teach quantifying the fragment having a mismatched base pair. Gifford teaches a similar method for detecting nucleic acid fragment having a mutation comprising: hybridizing at least one fragment fixed on a substrate with at least one fragment of which mutation is to be assayed (Column 4, lines 10-

23 and 66-67) and introducing a label into a fragment to be assayed to identify and quantify the fragment having a mismatch (Column 21, lines 1-10). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the mutation detection of Wagner et al. with the additional quantitation as taught by Gifford et al. for the expected benefit of detecting and quantifying heteroduplex fragments present as taught by Gifford et al. (Column 21, lines 7-10).

Regarding Claim 7, Wagner et al. teach a method for detecting nucleic acid fragment having a mutation wherein the label introduced into the nucleic acid fragment to be assayed for mutations (by adding the labeled mismatch-binding protein) and detecting the label of the are carried out in order to identify the fragment having a mutation (page 6, lines 19-24) but they do not teach the a label different from the label attached to the mismatch binding substance. Gifford et al. teach the similar method wherein the label introduced into the nucleic acid to be assayed for mutations produces a signal different from that produce by the label attached to the substance specifically binding to a mismatched base pair wherein quantification and identification of the fragment are performed simultaneously i.e. compare to identify and quantify (Column 21, lines 1-18).

Regarding Claim 8, Wagner et al. teach the method wherein the fragment to be assayed is labeled by being bound to a labeled substance which specifically binds to a mismatched base pair wherein the substance is labeled with at least one kind of substance selected from the group consisting of luminescent proteins, phosphorescent proteins, fluorescent proteins, luminescent substances, fluorescent substances, phosphorescent substances, radioactive substances, stable isotopes, antibodies, antigens enzymes and proteins (page 27, lines 22-32) but they do not teach the nucleic acid fragments are labeled. Gifford et al. teach the similar method wherein the nucleic acid fragments to be assayed are labeled with at least on kind of label selected from the group consisting of luminescent substances, fluorescent substances, phosphorescent substances, stable isotopes, radioactive substances (Column 10, lines 33-41).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the labeling taught by Wagner et al. with the additional label on the nucleic acid to be assayed as taught by Gifford et al. for the expected benefit of quantifying the heteroduplexes in a sample as taught by Gifford et al. (Column 21, lines 3-6).

Response to Arguments

8. Applicant argues that Gifford et al. do not remedy the deficiencies of Wagner et al. and therefore the combination of Wagner et al. and Gifford et al. do not teach or suggest the claimed invention. This argument is not found persuasive for the reasons stated above in ¶ 4 i.e. it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the DNA fixed on the substrate of Wagner et al. by fixing a full-length gene sequence on the substrate for the obvious benefit of detecting any and all mutations in a gene within a genomic sample.

9. Claims 9-18 & 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wagner et al. (WO 93/02216, published 4 February 1993) in view of Chirikjian et al. (U.S. Patent No. 5,763,178, filed 7 June 1996) and Goldrick (U.S. Patent No. 5,891,629, filed 28 September 1995).

Regarding Claim 9, Wagner et al. teach a method for detecting nucleic acid fragment having a mutation comprising: hybridizing at least one nucleic acid fragment, with at least one nucleic acid fragment of which a mutation is to be assayed; binding a labeled substance, said substance specifically binding to a mismatched base pair occurring between the hybridized fragments; and identifying a fragment bound by the labeled substance by detecting the label, thereby detecting a nucleic acid having a mutation (page 6, lines 1-25) wherein at least one fragment is fixed on a substrate (page 7, lines 4-8) and wherein the fragment fixed on the substrate (i.e. hybridization partner) is DNA prepared from any of source using any known technique e.g. naturally occurring DNA (page 16, lines 21-25). Wagner et al. do not teach the method wherein a substance which recognizes the mismatched base pair cleaves the

hybridized fragments and labeling the remaining fragments. However, Chirikjian et al. teach a similar method for detecting a nucleic acid fragment having a mutation comprising: hybridizing nucleic acid fragments with nucleic acid fragments of which a mutation is to be assayed treating a mismatched base pair occurring between the fragments with a substance specifically recognizing and cleaving the mismatched base pair labeling the cleaved fragments (Column 9, lines 33-38) and identifying the labeled fragment to thereby detect a nucleic acid having a mutation (Column 3, lines 8-28). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the mismatch binding protein of Wagner et al. with the mismatch binding protein which cleaves as taught by Chirikjian et al. for the expected benefit of eliminating the necessity of PCR amplification which introduces spurious point mutations and to thereby detect, identify and localize a nucleic acid having a point mutation accurately, economically and efficiently as taught by Chirikjian et al. (Column 6, lines 40-45).

Regarding Claim 10, Wagner et al. teach the method wherein said fragment is fixed on the substrate at the 5' end (page 19, lines 20-25) but they do not teach the 3' end of the fragment is blocked and the labeling of the fragment is performed by 3' end addition. However, Chirikjian et al. teach the similar method wherein the labeling of the cleaved fragment is by a 3' end addition reaction. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the labeling reaction of Wagner et al. with the 3' addition reaction of Chirikjian et al. based on mutation being detected for the expected benefit of detecting a point mutation accurately, economically and efficiently as taught by Chirikjian et al. (Column 6, lines 40-45).

Regarding Claim 11, Wagner et al. teach the method wherein the binding substance is MutS (page 6, lines 29-31) but they do not teach the binding substance is a nuclease. However, Chirikjian et al. teach the similar method wherein the binding substance is a nuclease (Column 7, lines 1-19). It would have been obvious to one of ordinary skill in the art

at the time the claimed invention was made to modify the MutS binding substance of Wagner et al. with the nuclease as taught by Chirikjian et al. based on mutation being detected for the expected benefit of detecting a point mutation accurately, economically and efficiently as taught by Chirikjian et al. (Column 6, lines 40-45).

Regarding Claim 12, Chirikjian et al. teach the similar method wherein the mismatch binding substance is a nuclease comprising numerous nuclease enzymes known in the art (Column 7, lines 1-25) but they do not specifically teach the nuclease is S1 nuclease, Mung bean nuclease or RNase H. However, Goldrick teach a similar method for detecting a mutation comprising: hybridizing a nucleic acid fragment with a fragment to be assayed; treating a mismatched base pair with a substance specifically recognizing and cleaving the mismatch base pair to cleave; and identifying the cleaved fragment to identify the mutated fragment wherein the cleaving substance is selected from S1 nuclease and Mung bean nuclease (Column 15, lines 2744). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the mismatch-bind substance of Wagner et al. and Chirikjian et al. with functionally equivalent nuclease i.e. S1 nuclease and/or Mung bean nuclease taught by Goldrick based on available reagents, mutation of interest and desired results to optimize experimental conditions to thereby maximize experimental results. The courts have further stated with regard to chemical homologs that the greater the physical and chemical similarities between the claimed species and any species disclosed in the prior art, the greater the expectation that the claimed subject matter will function in an equivalent manner (see *Dillon*, 99 F.2d at 696, 16 USPQ2d at 1904).

Regarding Claim 13, Chirikjian et al. teach the similar method wherein the labeling is performed by an enzyme reaction utilizing a label i.e. a gylcosylase-associated label (Column 9, lines 33-37).

Regarding Claim 14, Chirikjian et al. teach the similar method wherein the reaction is 3' addition (Column 9, lines 33-37).

Regarding Claim 15, Chirikjian et al. teach the similar method wherein the fragment is labeled with a fluorescent substance (Column 9, lines 35-37).

Regarding Claim 16, Chirikjian et al. teach the similar method wherein introducing a label into the fragment to be assayed are carried out in order to detect and quantify the fragment having a mismatched base (Column 9, lines 58-65).

Regarding Claim 17, Chirikjian et al. teach the similar method wherein quantification and identification of the fragment are simultaneously performed (Column 9, lines 39-52).

Regarding Claim 18, Chirikjian et al. teach the similar method wherein the fragment is labeled with a fluorescent substance (Column 9, lines 35-37).

Regarding Claim 22, Wagner et al. teach the method wherein the nucleic acid is cDNA (page 13, lines 4-9).

Regarding (New) Claim 33, Wagner et al. teach a method for detecting nucleic acid fragment having a mutation comprising: providing at least one polynucleotide fixed on a substrate; and a sample comprising at least one nucleic acid fragment; hybridizing said fragment to said polynucleotide; treating a mismatched base pair occurring between said hybridized fragment and polynucleotide with a substance that specifically recognizes the mismatch; labeling the fragment; and identifying the labeled fragment to thereby detect a nucleic acid having a mutation (page 6, line 1-page 7, line 8) and wherein the fragments have all of a sequence of a full-length gene (page 6, lines 25-27). Wagner et al. do not teach the method wherein a substance which recognizes the mismatched base pair cleaves the hybridized fragments and labeling the remaining fragments. However, Chirikjian et al. teach a similar method for detecting a nucleic acid fragment having a mutation comprising: hybridizing nucleic acid fragments with nucleic acid fragments of which a mutation is to be assayed treating a mismatched base pair occurring between the fragments with a substance specifically recognizing and cleaving the mismatched base pair labeling the cleaved fragments (Column 9, lines 33-38) and identifying the labeled fragment to thereby detect a nucleic acid having a

mutation (Column 3, lines 8-28). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the mismatch binding protein of Wagner et al. with the mismatch binding protein which cleaves as taught by Chirikjian et al. for the expected benefit of eliminating the necessity of PCR amplification which introduces spurious point mutations and to thereby detect, identify and localize a nucleic acid having a point mutation accurately, economically and efficiently as taught by Chirikjian et al. (Column 6, lines 40-45).

Response to Arguments

10. Applicant argues that Chirikjian et al. and Goldrick do not remedy the deficiencies of Wagner et al. and therefore the combination of Wagner et al., Chirikjian et al. and Goldrick et al. do not teach or suggest the claimed invention. This argument is not found persuasive for the reasons stated above in ¶ 4 i.e. it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the DNA fixed on the substrate of Wagner et al. by fixing a full-length gene sequence on the substrate for the obvious benefit of detecting any and all mutations in a gene within a genomic sample.

11. Claims 23-25 & 27are rejected under 35 U.S.C. 103(a) as being unpatentable over Wagner et al. (WO 93/02216, published 4 February 1993) in view of Zoltukhin et al. (U.S. Patent No. 5,874,304, filed 18 January 1996) and Fleck et al. (Nucleic Acids Research, 1994, 22(24): 5289-5295).

Regarding Claim 23, Wagner et al. teach a substance specifically bindable to a mismatched base pair wherein said substance is labeled (page 7, lines 10-16) but they do not teach the label is GFP. However, GFP labeled proteins were known in the art at the time the claimed invention was made as taught by Zoltukhin et al. who teaches the advantages of GFP i.e. it does not require cofactors or substrates and it is small in size (Column 1, lines 52-59 and Column 8, lines 22-27). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the GFP label of Zoltukhin et al. to the labeled

mismatched base pair binding substance of Wagner et al. for the advantages of GFP taught by Zoltukhin et al. i.e. GFP is small in size and does not require cofactors or substrates (Column 1, lines 52-59 and Column 8, lines 22-27).

Regarding Claim 24, Wagner et al. teach a substance specifically bindable to a mismatched base pair wherein said substance is labeled wherein the substance is the MutS protein or a functional derivative thereof (page 6, lines 19-31) but they do not teach the mismatch binding protein binds a c/c mismatch. However, c/c mismatch binding proteins were well known in the art at the time the claimed invention was made as taught by Fleck et al. who teach the MutS homologue of *Schizosaccharomyces pombe*, *swi*4 which specifically binds to c/c mismatched base pairs (page 5292). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify mismatch binding protein, mutS of Wagner et al. with the mutS homologue taught by Fleck et al. for the expected benefit of base-specific mismatch binding as taught by Fleck et al. (page 5294, last paragraph).

Regarding Claim 25, Wagner et al. teach a substance specifically bindable to a mismatched base pair wherein said substance is labeled wherein the substance is the MutS protein or a functional derivative thereof (page 6, lines 19-31) but they do not teach the mismatch binding protein binds a c/c mismatch. However, c/c mismatch binding proteins were well known in the art at the time the claimed invention was made as taught by Fleck et al. who teach the MutS homologue of *Schizosaccharomyces pombe*, swi4 which specifically binds to c/c mismatched base pairs (page 5292). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify mutS mismatch binding protein taught by Wagner et al. with the mutS homologue of Fleck et al. for the expected benefit of base-specific mismatch binding as taught by Fleck et al. (page 5294, last paragraph).

Regarding Claim 27, Wagner et al. the substance specifically binding to a mismatched base pair is labeled with at least one kind of substance selected from the group consisting of luminescent proteins, phosphorescent proteins, fluorescent proteins, luminescent substances,

fluorescent substances, phosphorescent substances, radioactive substances, stable isotopes, antibodies, antigens enzymes and proteins (page 27, lines 22-32).

Response to Arguments

12. Applicant argues that Zoltukhin et al. and Fleck et al. do not remedy the deficiencies of Wagner et al. and therefore the combination of Wagner et al, Zoltukhin et al. and Fleck et al. do not teach or suggest the claimed invention. This argument is not found persuasive for the reasons stated above in ¶ 4 i.e. it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the DNA fixed on the substrate of Wagner et al. by fixing a full-length gene sequence on the substrate for the obvious benefit of detecting any and all mutations in a gene within a genomic sample.

Response to Declaration

13. The declaration filed on 30 July 2001 under 37 CFR 1.131 is sufficient to overcome the Wagner et al. reference.

Dr. Yasushi argues that Wagner et al. do not teach or suggest the use of a DNA with the sequence of a full-length gene as a hybridization partner. Dr. Yasushi states that it is his understanding of Wagner et al. that the hybridization partner is an EST or shotgun fragments and that the standard methods referred to in Example III of Wagner et al. do not include preparation of full-length cDNAs or full-length genes. These arguments are not found persuasive because as stated above, Wagner et al. specifically that teach their hybridization partner is prepared using any known techniques and from any source e.g. naturally occurring DNA. Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the DNA fixed on the substrate of Wagner et al. by fixing a full-length gene sequence on the substrate for the obvious benefit of detecting any and all mutations in a gene within a genomic sample.

Dr. Yasushi also argues that the "tiling method" of Wagner et al. require a high number of overlapping fragments each fixed on a support in contrast to the claimed invention which requires only one full-length DNA. This argument is not found persuasive because Wagner et al. specifically teach the there "is not upper limit on the size of the hybridization partner" (page 17, line 4). Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the unlimited sequence length teaching of Wagner et al. to thereby fix sequences having a full-length gene or cDNA for the obvious benefit of detecting any and all mutations in a gene within a genomic sample.

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:45 TO 4:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
September 27, 2001

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600
9/28/01